REMARKS/ARGUMENTS

The Office Action mailed September 6, 2007 has been carefully reviewed. Reconsideration of this application, as amended and in view of the following remarks, is respectfully requested. Claims 1-17 appeared in the application as filed. Claims 1-10 are withdrawn from consideration as a response to a restriction requirement. Claims 12 and 14 have been cancelled. The claims presented for examination are: claims 11, 13, and 15-17.

35 U.S.C. § 112 Rejection

In numbered paragraph 4 of the Office Action mailed September 6, 2007, claims 11, 13, and 15-17 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action mailed September 6, 2007 stated:

> "Claim 11 recites "providing fragments of length n (n-mers)....that correspond to the virtual fragments" and "arraying ... fragments into groups." It is not clear whether these steps occur *in silico* or *in vitro*. More specifically, it is not clear whether the providing step intends to provide the fragments as part of the virtual breaking and subsequent temporal separation steps or if these fragments are provided for use in the in *vitro* reassembly steps. It is also not clear whether arraying step intends to purify/separate actual DNA fragments into groups (e.g., into different tubes, parts of an array, *etc.*) or "virtually" array fragments by using a computer program. Since the relationship between the method steps is not clear, claims 11, 13, and 15-17 are indefinite. It is noted that if the providing and arraying steps are intended to *recite in vitro* steps, inclusion of the words "in vitro" in these steps would overcome the above rejection.
>
> Claim 15 is further indefinite because not all of the terms appearing in the newly recited formula are defined in the claim. More specifically, the terms v, and p, are not defined."

Applicants have cancelled claims 13 and 15. Applicants have amended claims 11 and 15 to clarify that the arraying steps recite *in vitro* steps. The words "in vitro" have been added in these steps to overcome the rejection as indicated in the Office Action mailed September 6, 2007. Applicants believe that the amendment overcomes the rejection (claims 11, 16, and 17 remain as claims presented for examination) under 35 U.S.C. § 112, second paragraph, and that a complete response to the rejection has been provided.

35 U.S.C. § 102(e) Rejection Claims 11 and 13-15 – Evans Reference

In numbered paragraph 6 of the Office Action mailed September 6, 2007, claims 11 and 13 were rejected under 35 U.S.C. § 102(e) as being anticipated by the Evans reference (US 2003/0087238).

Claim 13 has been cancelled. Applicant believes the invention claimed in amended claim 11 is not anticipated by the Evans reference. The standard for a 35 U.S.C. § 102 rejection is stated in RCA Corp. v. Applied Digital Systems, Inc., 221PQ 385, 388 (d. Cir. 1984) "Anticipation is established only when a single prior art reference discloses, either expressly or under principles of inherency, each and every element of a claimed invention." Applicant points out that that a number of elements of Applicants' amended independent claim 11 are not found in the Evans reference. For example, the following elements of Applicants' amended independent claim 11 are not found in the Evans reference:

> "assembling groups in vitro by assembling said groups into double-strand DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase wherein said step of separating said DNA sequence segments temporally and said step of assembling said groups into double-strand DNA molecules of predetermined base-pairs is accomplished by said DNA sequence segments being added gradually, in an order that is predicted computationally to minimize errors to produce said DNA molecule of user-defined sequence," or

"wherein said step or assembling said groups into double-strand DNA molecules utilizes starting oligos of length n (n-mers) where n is an odd number."

Since the elements described above are not found in the Evans reference, the Evans reference does not support a 35 U.S.C. § 102(e) rejection of Applicants' amended claim 11 and the rejection should be withdrawn.

35 U.S.C. § 102(e) Rejection Claims 11 and 13-15 – Evans Reference

In numbered paragraph 7 of the Office Action mailed September 6, 2007, claims 15-17 were rejected under 35 U.S.C. § 102(a) and 102(e) as being anticipated by the Evans reference (US 2003/0087238).

Claim 15 has been cancelled. Applicant believes the invention claimed in dependent claims 16 and 17 is not anticipated by the Evans reference. The standard for a 35 U.S.C. § 102 rejection is stated in RCA Corp. v. Applied Digital Systems, Inc., 221PQ 385, 388 (d. Cir. 1984) "Anticipation is established only when a single prior art reference discloses, either expressly or under principles of inherency, each and every element of a claimed invention." Applicant points out that that a number of elements of Applicants' amended independent claim 11 and dependent claims 16 and 17 are not found in the Evans reference. For example, the following elements of Applicants' amended independent claim 11 and dependent claims 16 and 17 are not found in the Evans reference:

"assembling groups in vitro by assembling said groups into double-strand DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase wherein said step of separating said DNA sequence segments temporally and said step of assembling said groups into double-strand DNA molecules of predetermined base-pairs is accomplished by said DNA sequence segments being added gradually, in an order that is predicted

computationally to minimize errors to produce said DNA molecule of user-defined sequence," or

"wherein said step or assembling said groups into double-strand DNA molecules utilizes starting oligos of length n (n-mers) where n is an odd number," or

"wherein said starting oligos of length n-mers where n is an odd number are of a size n+1, n+2, etc."

Since the elements described above are not found in the Evans reference, the Evans reference does not support a 35 U.S.C. § 102(e) rejection of Applicants' dependent claims 16 and 17 and the rejection should be withdrawn.

35 U.S.C. § 103 Rejection- Selifonov & Evans

In numbered paragraph 9 of the Office Action mailed September 6, 2007, claims 11, 13-15, and 17 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Selifonov reference (WO 00/42560) in view of the Evans reference (US 2003/0087238).

Applicants have cancelled claims 13, 14, and 15. Applicants believe the invention claimed in amended independent claim 11 and dependent claim 17 is patentable and that the Selifonov reference and the Evans reference do not support a 35 U.S.C. § 103(a) rejection.

Applicants' Invention of Claims 11 and 17

Applicants' invention of claims 11 and 17 is a method of producing a DNA molecule of 1-10 kilobases of user-defined sequence from short oligos of length n (n-mers). The claimed method comprises a specific combination of steps. The specific combination of steps is not shown or suggested by either the Selifonov reference or the Evans reference. Applicants' original Figure 4

reproduced below and the description of the system 400 from Applicants' original specification illustrate the claimed invention.

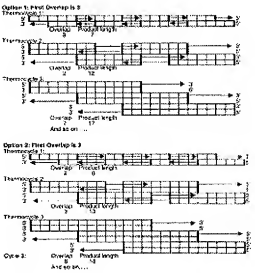

FIG.4

Applicants' invention of claims 11 and 17 is a method of producing a DNA molecule of 1-10 kilobases of user-defined sequence from short oligos of length n (n-mers) that includes the step of assembling groups in vitro by assembling said groups into double-strand DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase wherein said step of separating said DNA sequence segments temporally and said step of assembling said groups into double-strand DNA molecules of predetermined base-pairs is accomplished by said DNA sequence segments being added gradually, in an order that is predicted computationally to minimize errors to produce said DNA molecule of user-defined sequence, and wherein said step or assembling said groups into double-strand DNA molecules utilizes starting oligos of length n (n-mers) where n is an odd number.

Use of odd-sized starting oligos - Referring now to FIG. 4, another embodiment of a system of creating long DNA sequences, e.g., 1-10 kilobases, from short oligos of length n (n-mers) of the present invention is illustrated. The system is designated generally by the reference numeral 400. The system of

parallel synthesis 400 provides a process for making very long (greater than is possible with conventional phosphoramidite chemistry) DNA of user-defined sequence. The method begins by using computational techniques to break the desired sequence into fragments of defined size.

These n-base fragments are then arrayed in groups of n-base oligonucleotides and assembled into double-strand DNA molecules using DNA polymerase. The starting oligos may be of size n, where n is an odd number. The desired, hybridizing overlaps between oligos in the first thermocycle of PCR may be specified by the user. Table 1 gives a few examples of the overlap length, oligo length, and number of polymerized bases for several scenarios of starting oligo size and overlap in the first thermocycle, and the formula for computing these variables. The products of the reactions in the first tier of PCR reactions (each PCR reaction involves many thermocycles) are then combined, in as many steps as necessary, and assembled by polymerase into still-longer molecules, until the final desired product is assembled. The final product is then amplified using PCR.

The assembly process is substantially the same as the process called DNA shuffling. It is similar to PCR in that there is a template, a primer, a DNA polymerase, and the attendant nucleotides and buffers. It is dissimilar to PCR in that the primer and template are the same entities – the n-mers themselves. Following the parallel assembly process, the final product can be amplified by PCR. Any DNA polymerase commonly used for PCR can be used for this purpose.

The system 400 is similar to the system 300 described above and illustrated in FIG. 3; however, in the system 400, the starting oligos may be of odd length instead of even length. That is, in the system 300, the oligos, or n-mers, are of even length equal to n with a hybridizing overlap between

complementary oligos of length n/2 in the first two thermocycles. In contrast, in the system 400, the length n may be odd, and the overlap length between hybridizing oligos may be specified by the user.

Prima Facie Case of Obviousness Has Not Been Established

The rejection of independent claim 11 and dependent claim 17 under 35 U.S.C. § 103(a) is respectfully traversed. The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966) that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) include, "Ascertaining the differences between the prior art and the claims at issue." The Examiner bears the initial burden of factually supporting a *prima facie* conclusion of obviousness (M.P.E.P. Section 2142). Three basic criteria must be met in order for the Examiner to establish a *prima facie* case of obviousness. The prior art reference (or reference when combined) must teach or suggest all the claim limitations. There must be a reasonable expectation of success with the proposed combination. The Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

The Selifonov Reference

The Selifonov reference is International Patent No. WO 00/42560. The system of the Selifonov reference is an "in silico" DNA shuffling technique, in which part, or all, of a DNA shuffling procedure is performed or modeled in a computer system, avoiding (partly or entirely) the need for physical manipulation of nucleic acids. The system is described in the Selifonov reference specification and the Selifonov reference specification Fig. 1A reproduce below.

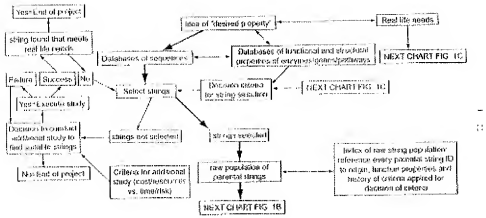

Fig. 1A

A set of flow schematics which provide a general representation of an exemplary process of Directed Evolution (DE) by GAGGS are enclosed (Figs. 1-4). Fig. 1 provides an example decision making process from an idea of a desired property to selection of a genetic algorithm. Figure 2 provides a directed evolution decision tree from selection of the genetic algorithm to a refined library of parental character strings. Figure 3 provides example processing steps from the refined parental library to a raw derivative library of character strings. Figure 4 processes the raw character strings to strings with a desired property.

Generally the charts are schematics of arrangements for components, and of process decision tree structures. It is apparent that many modifications of this particular arrangement for DEGAGGS, e.g., as set forth herein, can be developed and practiced. Certain quality control modules and links, as well as most of the genenic artificial neural network learning components are omitted for clarity, but will be apparent to one of skill. The charts are in a continuous arrangement, each connectable head-to tail. Additional material and implementation of individual GO modules, and many arrangements of GOs in working sequences and trees, as used in GAGGS, are available in various software packages. Suitable references

describing exemplar existing software are found, e.g., at http://www.aic.nrl.navy.mil/galist/ and at http://www.cs.purdue.edu/coast/archive/clife/FAQ/www/Q20-2.htm. It will be apparent that many of the decision steps represented in Figs. 1-4 are performed most easily with the assistance of a computer, using one or more software program to facilitate selection/decision processes.

References Do Not Teach All Claim Limitations

The criteria that prior art reference, or references when combined, must teach or suggest all the claim limitations has not been met. The Seligonov et al reference and the Evans reference do not disclose many Applicants' claim limitations. The Seligonov et al reference and the Evans reference do not disclose the limitations of Applicants' claims 11 and 17 identified below.

> "assembling groups in vitro by assembling said groups into double-strand DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase wherein said step of separating said DNA sequence segments temporally and said step of assembling said groups into double-strand DNA molecules of predetermined base-pairs is accomplished by said DNA sequence segments being added gradually, in an order that is predicted computationally to minimize errors to produce said DNA molecule of user-defined sequence," or

> "wherein said step or assembling said groups into double-strand DNA molecules utilizes starting oligos of length n (n-mers) where n is an odd number."

Since Applicants' combination of steps of amended independent claim 11 and dependent claim 17 identified above are not shown by the references it is clear that combining the references would not produce Applicants' invention. The fact that the two references fail to show the combination of elements of Applicants' amended independent claim 11 and dependent claim 17 identified above make it clear that there could not be a combination of the two references

that would produce Applicants' invention. Accordingly, the Examiner has not factually supported a *prima facie* case of obviousness and the rejection should be withdrawn.

No Reasons for Combining Selifonov and Evans

The criteria that the Examiner must provide reasons for modifying the reference has not been established. The Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

The rejection in the Office Action mailed September 6, 2007 does not provide an explanation of how or why the Selifonov and Evans references would be combined. Thus, the Selifonov and Evans references in the Office Action mailed September 6, 2007 fails to support a rejection of claims amended independent claim 11 and dependent claim 17 under 35 U.S.C. § 103(a), and the rejection should be withdrawn.

35 U.S.C. § 103 Rejection – Selifonov, Evans, and Murphy

In numbered paragraph 10 of the Office Action mailed September 6, 2007, claim 16 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Selifonov reference (WO 00/42560) and Evans reference (US 2003/0087238) in view of the Murphy et al reference (USPN 6,994,963.

Prima Facie Case of Obviousness Has Not Been Established

The rejection of independent claim 11 and dependent claim 17 under 35 U.S.C. § 103(a) is respectfully traversed. The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966) that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a)

include, "Ascertaining the differences between the prior art and the claims at issue." The Examiner bears the initial burden of factually supporting a *prima facie* conclusion of obviousness (M.P.E.P. Section 2142). Three basic criteria must be met in order for the Examiner to establish a *prima facie* case of obviousness. The prior art reference (or reference when combined) must teach or suggest all the claim limitations. There must be a reasonable expectation of success with the proposed combination. The Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

References Do Not Teach All Claim Limitations

The criteria that prior art reference, or references when combined, must teach or suggest all the claim limitations has not been met. The Seligonov et al reference and the Evans reference and the Murphy reference do not disclose many Applicants' claim limitations. The Seligonov et al reference and the Evans reference do not disclose the limitations of Applicants' amended independent claim 11 and amended dependent 16 identified below.

> "assembling groups in vitro by assembling said groups into double-strand DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase wherein said step of separating said DNA sequence segments temporally and said step of assembling said groups into double-strand DNA molecules of predetermined base-pairs is accomplished by said DNA sequence segments being added gradually, in an order that is predicted computationally to minimize errors to produce said DNA molecule of user-defined sequence," or

> "wherein said step or assembling said groups into double-strand DNA molecules utilizes starting oligos of length n (n-mers) where n is an odd number," or

"wherein said starting oligos of length n-mers where n is an odd number are of a size n+1, n+2, etc."

Since Applicants' combination of steps of amended independent claim 11 and dependent claim 16 identified above are not shown by the references it is clear that combining the references would not produce Applicants' invention. The fact that the three references fail to show the combination of elements of Applicants' amended independent claim 11 and dependent claim 16 identified above make it clear that there could not be a combination of the three references that would produce Applicants' invention. Accordingly, the Examiner has not factually supported a *prima facie* case of obviousness and the rejection should be withdrawn.

No Reasons for Combining Selifonov and Evans and Murphy

The criteria that the Examiner must provide reasons for modifying the reference has not been established. The Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

The rejection in the Office Action mailed September 6, 2007 does not provide an explanation of how or why the Selifonov and Evans and Murphy references would be combined. Thus, the Selifonov and Evans and Murphy references in the Office Action mailed September 6, 2007 fails to support a rejection of claims amended independent claim 11 and dependent claim 17 under 35 U.S.C. § 103(a), and the rejection should be withdrawn.

SUMMARY

The undersigned respectfully submits that, in view of the foregoing amendments and the foregoing remarks, the rejections of the claims raised in the Office Action dated September 6, 2007 have been fully addressed and overcome, and the present application is believed to be in condition for allowance. It is respectfully requested that this application be reconsidered, that the claims be allowed, and that this case be passed to issue. If it is believed that a telephone conversation would expedite the prosecution of the present application, or clarify matters with regard to its allowance, the Examiner is invited to call the undersigned attorney at (925) 424-6897.

Respectfully submitted,

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Livermore, California
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